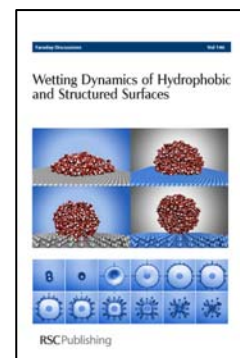


Faraday Discussions



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Exploring nanoscale hydrophobic hydration

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In this lecture, aspects of the hydration of hydrophobic interfaces that are emergent nanoscale properties of the interface chemical structure are discussed. General results inferred from systematic computational studies are emphasized, with a central theme focusing on the separate roles of surface topography and surface chemistry. The roles of surface curvature, polarity, and chemical heterogeneity, as well as the important role of solvent thermodynamic state are considered. The potential importance of understanding evolved natural biological interfaces on the same basis as model synthetic surfaces is pointed out, and progress in this direction is discussed.

1. Introduction

The phenomena to be discussed at the present *Faraday Discussion* 146 are remarkable. First and foremost in this regard is the fact that the wetting of an interface remains a topic of current and intense study on such a remarkably wide range of length and time scales. This range reflects the fact that the behavior observed initiates with molecular-scale phenomena, but that the emergent behavior of an interface is not simply predictable based on the properties of the hydration of small molecules alone. Indeed, both the chemical interactions occurring on a molecular level and the topography of a surface on a nano- to micro-scale are important determinants of the degree of surface hydrophobicity and of the dynamics of a liquid drop on such a surface. Correspondingly, studies addressing these phenomena on a variety of scales, *via* frameworks that range in detail from atomic coordinates to hydrodynamic fields, underlie progress toward fully understanding wetting broadly.

In this Introductory Lecture, I will address only one end of this scale, the nanoscale, and attempt to summarize what I believe to be the state of progress in understanding that scale. In particular, a considerable amount of effort has been invested in just the last several years in developing a *systematic* understanding of the relationship between the nanoscale chemical structure of interfaces and both the nanoscale hydration structure, on the one hand, and macroscopic measures of hydrophobicity, such as contact angle, on the other. Understanding the impact of molecular polarity, when coupled to interfacial molecular topography, is a particularly important element. An understanding of the role of chemical heterogeneity is also important, particularly considering that bio-macromolecular surfaces are both highly functional and heterogeneous.

The literature in this area is extensive and it is not possible to discuss or even cite all of the relevant work that underlies the current state of knowledge. The intent here is to capture certain major points that are relevant to nanoscale hydrophobic hydration and to point to particular work in the literature that illustrates these. A more in depth discussion can be found in the articles that are cited here.

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2. Generic effects of exclusion

This summary will first consider what I call exclusion surfaces, surfaces that, in the simplest case, have no chemical character but only present an impermeable interface to water. These are the ultimate non-polar, hydrophobic, surfaces and provide a useful theoretical construction and systematic starting point. The essential behavior of such surfaces is a function of the radius of curvature, with the hydrogen bonding network between water molecules fully capable of accommodating small radius, molecular scale, interfacial features (under ambient conditions) by restricting solvent orientations to those with hydrogen (H-)bonding directions either tangential to or pointing away from such surfaces, as in solid clathrate hydrates.¹ For features with characteristic radius larger than of the order of 1 nm, the H-bond strain induced in a tetrahedral network is too high, some H-bond rupture is unavoidable, and an inverted structure appears with a propensity for one H-bond direction to point inwards to the interface and three to point toward the bulk liquid.²⁻⁵ This optimized organization leads with increasing radius of curvature to a decreasing solvent density in immediate contact with a simple exclusion surface.⁶⁻⁸ In general, if one examines the dependence of solvation free energy on molecular size, one finds a cross-over with increasing size to a regime that is largely dependent on solute surface area. This phenomenon is, however, not limited to aqueous or even H-bonded liquids, but reflects more generally the stability of the liquid interface. The same behavior is seen for a simple Lennard-Jones liquid for thermodynamic states that lie near the coexistence curve, with the free energy of cavity formation dominated by enthalpic penalties.^{6,9}

What has become clear as a result of a number of studies is, first, that this depression of density at the interface is not a general primary characteristic of hydrophobic hydration.⁷ The density is sensitive to the existence of attractive forces exerted by the surface, and the observation of solvent “drying” at a single surface does not follow the chemistry in a simple way.¹⁰ More recent studies indicate that the magnitude of solvent density *fluctuations*, or local solvent compressibility, is a more general indicator of hydrophobicity,¹⁰⁻¹⁴ and it is one that increases with surface radius of curvature for exclusion surfaces. A reduction in the work to create a void in the vicinity of the surface (and a corresponding free energy driving force for non-polar moieties to preferably reside there, compared to the bulk solvent) correlates with this increased density fluctuation,¹⁰ as one might expect. Correspondingly, those phenomena associated with enhanced compressibility are suppressed with increasing pressure, a result seen in several systems.^{10,15} It is worth noting that simulations of similar quantities for the solvent surrounding proteins¹⁶ yield an excess local solvent compressibility near protein apolar surfaces that is comparable to that found near model extended apolar surfaces.

3. Continuity of the scale of hydrophobicity

To chemists, the idea that the degree of hydrophobicity is a variable quality is a generally accepted concept, which has its origin in the variable atomic composition of molecular species and variations in their packing in materials. Computational studies of model systems have the ability to vary the various qualities of a surface completely independently of physical constraints, which can sometimes lead to additional insights. One example is a study carried out to understand the relationship between water contact angle, solvent structure, and surface polarity for a system where the nanoscale chemical homogeneity of the surface is constant.¹⁷ The surface used corresponded to hydroxylated silica (quartz) and only the polarity of the model surface was varied, by scaling of surface atom partial charges. Having restricted the variations in the surface, it was clear that the contact angle tracked the solvent orientational preferences nearly ideally, with the surface that exhibited a “neutral” contact angle of 90° also being that surface exhibiting a neutral preference for any

particular solvent orientation in proximity to the surface (in contrast to those described in Sec. 2). Perhaps of more interest, the orientational distributions observed at each level of polarity could be described by a superposition of those for the most polar and non-polar cases. This suggests that the two structures coexist in domains. This might be expected for an extended interface, based on the fact that the inverted structure with water H-bond loss, characteristic of an extended non-polar surface, is a result of optimizing the capacity of solvent to form water–water H-bonds, an inherently cooperative behavior.¹⁸

Given this correlation of contact angle with surface polarity, one might ask why fluorocarbon surfaces behave more hydrophobically than hydrocarbons.¹⁹ The C–F bond is relatively more polar than is a C–H bond, suggesting the opposite at first guess. The answer recalls the discussion above about the role of dispersive van der Waals attractive forces. Fluorocarbons are relatively large compared to hydrocarbons and so the density of attractive centers on a self-assembled layer or in a polymeric film of fluorocarbon is reduced compared to hydrocarbons. At the same time, fluorine is relatively less polarizable (with correspondingly smaller dispersive forces) than one would expect of other atoms of similar size, with the overall result that fluorocarbon surfaces are the more hydrophobic. This explanation takes no account of changes in solvation structure. It has been appreciated for many years that the hydration structure of extended hydrophobic surfaces is relatively insensitive to mild polar surface interactions,⁵ resulting from the very strong orientational preferences associated with satisfying solvent intermolecular H-bonding, already discussed. In fact, for weakly polar aprotic (non-network) solvents, fluorocarbon surfaces do appear to have enhanced attraction.²⁰

4. Hydration at non-ambient conditions

Because water is essential for terrestrial biology, the variation of thermodynamic state away from ambient temperature and pressure is sometimes neglected in consideration of aqueous systems. Nevertheless, it is widely appreciated that proteins that are taken from mesophilic species, adapted to ambient conditions, can be denatured not only by heating but also by high pressures or by low temperatures.²¹ The implication is that this is a result of changes in the strength of hydrophobic interactions. We have already touched on the impact of interfaces on local compressibility, *i.e.*, on the differential response to pressure of interfacial water compared to bulk water, and the resulting enhancement of hydrophobic interactions. In fact, studies show that it is the translational ordering of water that is most responsive to pressure while the orientational order, dictated by the strong H-bond network within water, is relatively refractory.¹⁵ At a hydrophilic surface, where H-bonds also form between the surface and water, one finds that neither type of order is responsive to pressure.¹⁵ The complementary perturbation associated with isobaric cooling to temperatures below ambient show remarkably similar solvent response to those seen in isothermal compression;²² the solvent contact density with a hydrophobic surface is increased with decreasing temperature with little change in solvent orientational order at that surface, while hydrophilic surfaces show little structural change in solvation, beyond a sharpening of structural features. Hence, these model interfacial systems very clearly manifest the characteristics of decreasing hydrophobicity with increasing pressure and/or decreasing temperature, starting from ambient conditions.

5. Impact of chemical heterogeneity

For a heterogeneous patterned surface, hydration at the boundaries between hydrophilic and hydrophobic regions could well be expected to be of special significance. What is the resolution of such an atomic-scale boundary when seen from a solvent-mediated perspective? Correspondingly, one could ask whether the resolution that

can be achieved in chemically patterning surfaces can be resolved in self-assembly of hydrophobic surfaces in solution. We find from the study of nanoscale patterned surfaces²³ that boundary lines defined by hydrophilic sites, in fact, are nearly fully resolved by the solvent density, except at very low hydrophilic site coverage. In fact, the presence of polar surface moieties at a boundary is found to be amplified by the solvent, with an excess hydration density at such boundaries compared to a uniform hydrophilic surface.²³ One consequence of this enhanced hydration is that sub-nanometre hydrophilic or hydrophobic patches (*e.g.*, involving only one or a few molecular surface sites) can become less distinct when resolved in terms of solvent density.^{23,24}

Of course, since pressure and temperature blur the difference between hydrophobic and hydrophilic surfaces, the resolution of boundary lines is greatly reduced as pressure increases or temperature decreases.^{22,23} This appears closely related to protein denaturation, already mentioned above.

6. Confinement between nanoscale hydrophobic surfaces

It is well established that, at least for macroscopic hydrophobic surfaces, there exists a critical separation below which the vapor phase is thermodynamically favored over the liquid, as reviewed, for example, in ref. 25. The argument is based simply on the increasing relative importance of the interfacial free energy of the fluid interfaces, when the volume of bulk fluid lying between these interfaces is decreasing. For nanoscale surfaces, it is clear that one can also get such a drying between surfaces, and that some minimum size surface is needed to observe the effect.²⁶ Nevertheless, the thermodynamic effects of finite size and the kinetic barriers to formation of vapor phases have not been developed fully.²⁵ Within the limitations of typically nanosecond timescales associated with conventional molecular dynamics, it is, however, of interest to explore the phase behavior of confined water and its response to temperature, pressure, and surface chemistry. For water in contact with and confined by a pair of model nanoscale hydrophobic (silica) plates, such studies have been carried out.^{15,22,23,27} At ambient temperature, the results reveal a regime of inter-plate gaps ranging up to about 1 nm where water cavitation occurs between the plates at pressures where the bulk solvent remains mechanically stable. This regime of gaps d decreases with increasing pressure, as expected, until the gap size for hypothetical cavitation is smaller than the physical size of one molecular layer of water (at about 0.15 GPa for SPC/E water²⁸ at 300 K), where macroscopic fluid concepts are untenable. Interestingly, at these high pressures, a number of additional phase transitions involving new *solid* phases occur for the confined condensed phase at 300 K,²⁷ in analogy to the formation of bilayer ice first observed between unstructured hydrophobic plates.²⁹ As temperature is reduced, the coexistence line in the gap-pressure (d, P) plane between the vapor and condensed (liquid or solid) phases moves increasingly toward the limit of bulk stability, so that the region in d of vapor stability nearly vanishes at very low temperatures, while the region in d manifesting a stable bilayer solid increases.²²

7. Biological interfaces

Since proteins have evolved to form specific assemblies with each other, with other active biological molecules, and with metabolic substrates, it is of great interest to understand to what extent lessons learned about hydration of synthetic and natural surfaces can be profitably transferred between them. To this end, one model system, the dimer of the amphipathic polypeptide melittin, and its assembly in the crystallographic tetramer, has been examined in several simulation studies which address solvation structure and the impact of confinement.^{18,24,30,31,32} Some years ago, the hydration structure of the melittin dimer was examined from the perspective of the impact of extended hydrophobic surface.³⁰ It was found that the solvent adjacent

to a patch of “flat” hydrophobic surface did manifest the loss of H-bonding in water and the orientational structure seen in model extended interfaces. More recently, it was shown that if two dimers (fixed in their crystallographic geometries) were brought into close proximity along a vector that would bring them to the assembled crystal tetramer, a drying transition occurred, with solvent evacuating the gap between them in advance of dimer–dimer contact.³¹ It was further shown that protruding hydrophobic groups on the dimers were a critical element in that process; these tended to cutoff the solvent gap from the bulk solvent prior to contact.

In order to examine this apparent role of topography in more detail and to provide a means to put synthetic and natural systems on a comparable footing, a study was carried out involving a “flat” melittin dimer surface.³² To accomplish this, the protein interface was geometrically modified by shifting residues along the inter-dimer direction so that the contact interface between dimers became flat, while preserving the characteristic chemistry. The details are provided elsewhere.³² A very small area of dewetting was observed at the smallest inter-dimer gap where water might still enter, and this occurred in the region of the gap proximal to the previously identified flat hydrophobic surface. Nevertheless, it was demonstrated that the surface would wet for gaps only an Angstrom larger, for moderately increased pressures, or upon substitution of a single polar amino acid for a non-polar one on the dimer interface. These observations suggested that the flat, natural chemistry, surface was only marginally hydrophobic. Direct comparison of the solvent (*d,P*) phase diagrams, as well as solvent compressibilities, for the case of this natural chemistry interface with those for silica plates revealed a behavior for the protein-like case that was clearly intermediate between the synthetic hydrophobic and hydrophilic cases. The implication is that a prototypical hydrophobic protein surface, clearly involved in self-assembly, as evident in the crystal structure, need not be as hydrophobic as a simple Lennard-Jones (*e.g.*, alkyl) material in order to be functional.

8. Conclusions

The results just discussed suggest that nanoscale topography and chemical hydrophobicity can play equally important roles in natural system assembly and function. On a larger length scale, this is, of course, a guiding principle of superhydrophobic interface design, as the papers following in this Discussion demonstrate. Recent simulations probing the potential for drying in hypothetical gaps created at hydrophobic interfaces in multi-protein assemblies³³ show that even in systems selected as likely candidates, drying is not a common phenomenon. Earlier simulation results for hydration of the enzyme α -chymotrypsin³⁴ showed both that the nominally hydrophobic binding pocket at the active site is occupied by water (as was already established by experiment) and that it exhibited substantial amphipathic character when examined at atomic resolution, despite its selectivity for binding non-polar amino acid residues. Extending studies of the relationship between nanoscale topography and hydrophobicity to a broad set of synthetic surfaces as well as proteins appears well justified. Such a program to establish specific relationships between topography and hydrophobicity in natural and model self-assembled systems may well yield a scheme which one could readily extend to complex self-organizing synthetic systems.

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